

Amendments to the Specification

Please amend the paragraph appearing on page 11, line 10 to page 12, line 6 as follows:

--In contrast to the Fc Tag technology (Sledziewski et al., 1992 and 1998), with which secreted dimeric fusion proteins can be created, this timely invention disclosed herein enables the creation and secretion of soluble trimeric fusion proteins for the first time. Given the fact that a homotrimer has 3-fold symmetry, whereas a homodimer has only 2-fold symmetry, the two distinct structural forms theoretically can never be perfectly overlaid (~~Fig 1~~ Figures 1A-1D). As such, neither the homodimeric soluble TNF-R-Fc (e.g. Enbrel®), nor the soluble CD4-Fc fusion proteins, could have had an optimal interface for binding to their corresponding homotrimeric ligands, TNF- α and HIV gp120, respectively. In contrast, homotrimeric soluble TNF receptors and CD4 created by the current invention are trivalent and structurally have the potential to perfectly dock to the corresponding homotrimeric ligands. Thus, these trimeric soluble receptor analogs can be much more effective in neutralizing the biological activities of their trimeric ligands. With this timely invention, more effective yet less expensive drugs, such as trimeric soluble TNF-R and CD4 described in the preferred embodiments, can be readily and rationally designed to combat debilitating diseases such as arthritis and AIDS. Trimeric soluble gp120 can also be created with this invention, which could better mimic the native trimeric gp120 coat protein complex found on HIV viruses, and used as a more effective vaccine compared to non-trimeric gp120

antigens previously used. Also chimeric antibodies in trimeric form can be created with the current invention, which could endow greatly increased avidity of an antibody in neutralizing its antigen.--

Please amend the paragraph appearing on page 15, lines 1-4 as follows:

--**Fig. 5.** Quantitative analysis of the neutralizing activity of trimeric soluble human TNF-RII-T2 against human TNF- α . The experiment was carried out as Fig 4. ~~Fig. 4A.~~ Two hours after adding the Alamar Blue dye, the culture medium as indicted from each well was analyzed at OD575. The readings were normalized against wells with either no TNF- α (100% viability) added or with TNF- α without neutralizing agent (0% viability) added.--

Please amend the paragraph appearing on page 20, line 16 to page 21, line 4 as follows:

--Prior to this invention, nearly all therapeutic antibodies and soluble receptor-Fc fusion proteins, such as ~~Enbrel~~ Enbrel®, are dimeric in structure (~~Fig. 1~~ Figures 1A-1D). Although these molecules, compared to their monomeric counterparts, have been shown to bind their target antigens or ligands with increased avidity, it is predicted that they are still imperfect, due to structural constrains, to bind their targets that have a homotrimeric structure. Examples of such therapeutically important trimeric ligands include TNF family of cytokines and HIV coat protein gp120. Therefore, from a structural point of

view, it will be desirable to be also able to generate trimeric soluble receptors or antibodies, which can perfectly dock to their target trimeric ligands or antigens (~~Fig. 1~~ Figures 1A-1D), and thereby completely block the ligand actions. Such trimeric soluble receptors or chimeric antibodies are expected to have the highest affinity to their targets and thus can be used more effectively and efficiently to treat diseases such as arthritis and AIDS.--

Please amend the paragraph appearing on page 22, lines 4-16 as follows:

--To demonstrate the feasibility for making secreted trimeric fusion proteins, cDNA sequences encoding the entire C-propeptides of human $\alpha 1(I)$ containing either some glycine-repeat triple helical region (T0 construct, SEQ ID NOS:1-2), or no glycine-repeat with a mutated BMP-1 recognition site (T2 construct, SEQ ID NOS:3-4) were amplified by RT-PCR using EST clones purchased from the American Type Culture Collection (ATCC). The amplified cDNAs were each cloned as a Bgl II-XbaI fragment into the pAPtag2 mammalian expression vector (GenHunter Corporation; Leder et al., 1996 and 1998), replacing the AP coding region (~~Fig. 2~~ Figures 2A and 2B). The resulting vectors are called pTRIMER, versions T2 and T0, respectively. The vectors allow convenient in-frame fusion of any cDNA template encoding a soluble receptor or biologically active protein at the unique Hind III and Bgl II sites. Such fusion proteins have the collagen trimerization tags located at the C termini, similar to native pro-collagens.

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